REMARKS

Claims 19-22, 24-26, 29-31 and 33-36 are currently pending. Claims 23, 27, 28, 32, 37, 39, 42, 43, 44, 45 and 48 are cancelled herein without prejudice in order to advance prosecution, and Applicant reserves the right to pursue the subject matter of these claims in this or other applications, for example, divisional or continuation applications. The claims are amended to more particularly state the invention and to advance prosecution. The amendments are supported by the specification and original claims and do not constitute new matter. For example, the amendment of claim 19 to provide for prevention of chronic refractory rejection of lung transplants is supported by the instant specification at paragraph 1 (page 1 of the published application US20020006901 A1) and to provide for the use of one or more other immunosuppressive agent is supported by the instant specification at paragraph 28 (page 3 of the published application) and paragraph 46 (page 5 of the published application); the amendment of claim 25 to list pulmonary inflammatory disorders is supported by the instant specification at paragraph 38 (page 4 of the published application), and the amendment of claim 36 to recite T-cell mediated immune disorders is supported by the specification at paragraph 33 (page 4 of the published application). For the Examiner's convenience, a clean version of the claims, as amended, is attached hereto.

The Examiner has rejected claims 19-37, 39, 42-45, and 48 under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The Examiner has rejected claims 19-37, 39, 42-45, and 48 under 35 U.S.C. § 103(a) as being unpatentable over Adjei *et al.* (U.S. Patent No. 5,635,161) ("Adjei") and Waldrep *et al.* (U.S. Patent No. 5,958,378) ("Waldrep") in view of Knight *et al.* (U.S. Patent No. 5,049,388) ("Knight"), Gordon *et al.* (U.S. Patent No. 6,572,893) ("Gordon"), and Iacono *et al.* (Am. J.

Respir. Care Med., 1997, 155:1690-1698) ("Iacono"). For the reasons detailed below, the rejections should be withdrawn and the claims allowed to issue.

1. The Claims Are Supported By The Specification

The Examiner has rejected claims 19-37, 39, 42-45, and 48 under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The Examiner states that the phrase "non-encapsulated cyclosporine" lacks support in the application as originally filed.

The relevant claims have been amended either to omit reference to "non-encapsulated" or to recite "a dose of cyclosporine dissolved in an organic solvent." Support for this amendment can be found at page 20, line 16 to page 21, line 2. The rejected term "non-encapsulated" has been deleted from the claims. The specification clearly discloses the use of organic solvents to dissolve cyclosporine, thereby producing a cyclosporine *solution*- which is to say, a homogeneous distribution of cyclosporine in a solvent, *not* enclosed in liposomes . See the specification at, for example, page 20, lines 16-20 ("cyclosporine may be dissolved in any recognized physiologically acceptable carrier.... it is soluble in lipids and organic solvents."). Applicant submits that the claims as amended are fully described by the specification.

Applicant submits that the Examiner's rejection for lack of written description has been obviated, and respectfully requests that the rejection be withdrawn.

2. The Claims Are Not Obvious

The Examiner has rejected claims 19-37, 39, 42-45, and 48 under 35 U.S.C. § 103(a) as being unpatentable over Adjei *et al.* (U.S. Patent No. 5,635,161) ("Adjei") and Waldrep *et al.* (U.S. Patent No. 5,958,378) ("Waldrep") in view of Knight *et al.* (U.S. Patent No.

5,049,388) ("Knight"), Gordon *et al.* (U.S. Patent No. 6,572,893) ("Gordon"), and Iacono *et al.* (Am. J. Respir. Care Med., 1997, 155:1690-1698) ("Iacono"). The Examiner states that Waldrep and Adjei teach all of the limitations of the present invention except the non-encapsulated dosage form, the claimed dose levels, or the timing of the treatment. The Examiner contends that Knight, Gordon, and Iacono disclose the non-encapsulated dosage form, and that it would have been obvious for a person of ordinary skill in the art to modify the dosage and timing of the treatment to reach the present invention.

Applicant first note that the composition claims have been cancelled, without prejudice, in order to advance prosecution, thereby obviating this rejection as applied to compositions.

As regards the pending method claims, Applicant asserts that they are not obvious over the art. In support of Applicant's assertion that the claimed invention is not obvious, Applicant invites the Examiner's attention to Exhibits A-C, attached hereto. These references relate to a clinical trial involving inhaled cyclosporine, recently reported in the presitigious New England Journal Of Medicine. These references demonstrate that the clinical benefits of *prophylactic*, inhaled cyclosporine, administered together with conventional immunosuppressive agents, were unexpected and viewed by the medical community as exciting (see Exhibit B, an editorial entitled "A Breath of Fresh Air") and as holding great promise toward addressing a long-felt need.

Exhibit A, Iacono et al., 2006, "A Randomized Trial of Inhaled Cyclosporine in Lung-Transplant Recipients," N. Engl. J. Med. 354:141-150 ("Iacono 2006," where the first author is the inventor of the present application) reports the results of "a single-center, randomized, double-blind, placebo-controlled trial of inhaled cyclosporine initiated within six weeks after transplantation and given in addition to systemic immunosuppression." The trial

involved a total of 58 patients. The primary end point was the rate of histologic acute rejection. As regards that end-point, the results of the trial were negative- the rate of acute rejection was not significantly different between cyclosporine and placebo groups. However, other results were perhaps even more promising than if the initial goal had been achieved. The study showed that the use of inhaled cyclosporine improved survival and extended periods of chronic rejection-free survival. In discussing these results, Iacono 2006 states, in the paragraph bridging pages 148 and 149:

> Chronic rejection remains the leading cause of death after lung transplantation despite the use of systemic calcineurin inhibitors [citations]. The immunosuppressive effects of cyclosporine have been shown to be dose-dependent. However, high systemic levels of the drug cannot be achieved without significant toxicity, especially to the kidneys. We hypothesized that the inhalation of an aerosol cyclocporine would provide high pulmonary concentrations of the drug with minimal systemic toxicity, resulting in less acute and chronic rejection. This double-blind, placebo-controlled trial of inhaled cyclosporine given in addition to conventional immunosuppression after lung transplantation was negative with respect to its primary end point, since rates of acute rejection were similar in the group receiving cyclosporine and that receiving placebo. However, survival improved significantly with aerosol cyclosporine, as did the rate of chronic rejection-free survival (on the basis of both histologic and spirometric analysis).

The same issue of the New England Journal of Medicine contained an editorial by Malcolm M. DeCamp, Jr., M.D., a thoracic surgeon at Beth Israel Deaconess Medical Center in Boston (DeCamp, Jr., 2006, "Inhaled Cyclosporine - A Breath of Fresh Air?" N. Engl. J. Med. 354:191-193; "DeCamp"). By way of introduction, DeCamp restates the problem (at page 191):

> Newer drugs for the induction and maintenance of immunosuppression have lessened the severity and frequency of acute rejection [citations]. However, beyond the first year after engraftment, the rate of death among lung-transplant recipients has essentially remained unchanged between the 1980s and the present. At the five-year follow-up, nearly 50 percent of recipients are dead [citations].

With regard to the clinical trial reported in Iacono 2006, DeCamp states (at page 192]:

> Iacono and his colleagues from Pittsburgh exploited the unique interface of the lung with our world by delivering augmented immune therapy directly to the graft through the airways. They were able to do this without engendering an increase in pulmonary infection and without the risk of detectable systemic absorption and potential nephrotoxicity from larger amounts of calcineurin inhibitors. Previous attempts to achieve this effect with inhaled corticosteroids were unsuccessful. [citation] It would appear that inhaled cyclosporine might help at least delaying the onset of obliterative bronchiolitis and pushing the late-survival curves of lung transplant recipients toward those of heart, liver and kidney recipients.

According to DeCamp, to focus on the failure of the trial to demonstrate prevention of acute rejection "places a methodologic tree ahead of the forest." DeCamp concludes by stating (at page 193) "[t]hese results should be received enthusiastically by lung-transplant physicians and surgeons but need to be confirmed by a more broadly inclusive multicenter trial." As demonstrated by Exhibit C. Rauscher, May 23, 2006, "Aerosol Cyclosporine Preserves Lung Function in Transplant Recipients," Reuters Health:

> The data on aerosol cyclosporine's impact on survival and chronic rejection were presented to the U.S. F.D.A. in 2005 and the agency has requested a multicenter trial. Dr. Iacono is hopeful that the transplant community can work together to organize such a trial.

Exhibits A-C amply demonstrate that the clinical benefits of prophylactic aerosolized cyclosporine were received with "enthusiasm" by the scientific community - and were *not* regarded as obvious old news. The technology is considered to be sufficiently promising to warrant the FDA requesting a multicenter trial. If the present invention were obvious to the skilled artisan, the results of Dr. Iacono's clinical trial would not have been considered sufficiently newsworthy to be reported in the New England Journal of Medicine and the popular press. Applicant respectfully reminds the Examiner that the evidence of non-obviousness presented as Exhibits A-C must be considered in evaluating the patentability of the presently claimed invention.

Further, Applicant submits that the Examiner has not set forth a *prima facie* case of obviousness. To establish a *prima facie* case of obviousness, the Examiner must meet three criteria. The Examiner must establish that (1) there is some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) there is a reasonable expectation of success; and (3) the prior art reference (or references when combined) teach or suggest all the claim limitations. See MPEP §§ 706.02(j) and 2143. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q2d 1438 (Fed. Cir. 1991).

Applicant submits that Waldrep, Knight, and Adjei do not provide the suggestion or motivation to utilize non-liposomal forms of cyclosporine as recited in the claims, as amended. As noted above, the claims have been amended to recite "cyclosporine dissolved in an organic solvent," thereby excluding liposomes from the claim scope. In contrast, Waldrep, Knight, and Adjei utilize aerosolized compositions of cyclosporine encapsulated in liposomes; neither reference discloses that a cyclosporine composition which is not encapsulated in a liposome could be successfully administered in aerosol form. Accordingly, a person of ordinary skill in the art would not have the suggestion or motivation to utilize the aerosolized compositions of Waldrep, Knight, and Adjei to reach the present invention, because the present invention does not utilize liposomal compositions.

Similarly, while Gordon discusses non-liposomal drug compositions, Gordon does not provide any suggestion or motivation to utilize these compositions in aerosol form. A person of ordinary skill in the art would not be motivated to combine the non-liposomal compositions of Gordon with any of the liposomal compositions of Waldrep, Knight, and/or

Adjei to reach non-liposomal aerosol compositions. Accordingly, Gordon does not supply the suggestion or motivation to utilize non-liposomal aerosol compositions.

Applicant submits that there is no suggestion or motivation to administer aerosolized cyclosporine compositions prior to the onset of graft rejection. Iacono discloses the treatment of patients suffering from refractory graft rejection, where standard immunosuppressive treatments have failed, and accordingly only describes the use of aerosolized cyclosporine as a rescue treatment. See Iacono at page 1691, left column. As previously noted, Iacono discloses treatment of graft rejection after the graft rejection has already occurred, but does not provide any suggestion or motivation to utilize the aerosolized cyclosporine compositions before the graft rejection occurs. Although the Examiner states that

> "[O]ptimization of a result effective parameter is considered well within the skill of the artisan.... Nowhere in Iacono teaches or suggests that cyclosporine A had to be used long after the transplantation to be effective. A therapeutic agent known to be effective for treating a disorder, or a symptom would have been reasonably expected to be useful for a prophylactic treatment of such disorder or system."

Applicant notes that Iacono in fact states that "multidrug immunosuppressive regimens based on cyclosporine have been *imperfect in both prevention and treatment* of rejection" due to the toxic side effects of cyclosporine. See Iacono at page 1691, left column (emphasis added). Thus, a person of ordinary skill in the art could not assume that prevention of graft rejection via the administration of aerosolized cyclosporine prior to the onset of rejection would be successful, based upon a reference that discloses successful use of aerosolized cyclosporine as a rescue treatment. At best, Iacono suggests *trying* to utilize the aerosolized cyclosporine compositions to prevent graft rejection. However, "obvious-to-try" is not the standard for obviousness in accordance with 35 U.S.C. § 103. *In re Dow Chemical Co.*, 837 F.2d 469, 473 , 5 U.S.P.Q.2d 1529, 1532 (Fed. Cir. 1988); see also *In re O'Farrell*, 853 F.2d 894, 903, 7 U.S.P.Q.2d 1673, 1681 (Fed. Cir. 1988).

Furthermore, a mere statement that a person of ordinary skill in the art would be capable of arriving at the claimed invention is insufficient to establish a *prima facie* case of obviousness. MPEP § 2143.01 ("A statement that modification of the prior art to meet the claimed invention would have been 'well within the ordinary skill of the art at the time the claimed invention was made' because the references relied upon teach that all of the aspects of the claimed invention were individually known in the art is not sufficient to establish a *prima facie* case of obviousness without some objective reason to combine the teachings of the references.") (emphasis in original). In the present case, none of the references provides an objective reason to administer the aerosolized cyclosporine compositions before the onset of graft rejection, and, as noted above, Iacono indicates that the successful use of cyclosporine as a preventative treatment is unpredictable. Given the potential toxicity of cyclosporine, a clinician would need to think twice before administering the drug prophylactically.

Based upon the all foregoing, Applicant submits that the present invention is not obvious, because there is insufficient suggestion or motivation to combine the references cited by the Examiner to reach the present invention, and because the results of prophylactic administration of aerosolized cyclosporine were unexpected, as viewed by persons of skill in the art (and, if fact, by persons of extraordinary skill in the art). On this record, Applicant respectfully requests withdrawal of the rejection.

CONCLUSION

Entry of the foregoing amendments and remarks into the file of the above-identified application is respectfully requested. The Applicant believes that the inventions described and defined by claims 19-20, 22-26, 28-31, 33-36, 39, 42-45, and 48 are patentable over the rejections of the Examiner. Withdrawal of all rejections and reconsideration of the amended claims is requested. An early allowance is earnestly sought.

Respectfully submitted,

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